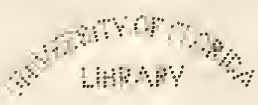
DERIVATIVES OF PIPERAZINE V

By

ALLEN T COLE

A Dissertation Presented to the Graduate Council of
The University of Florida
In Partial Fulfilment of the Requirements for the
Degree of Doctor of Philosophy



UNIVERSITY OF FLORIDA
August, 1935

TABLE of CONTENTS

INTRODUCTION

Since both imino hydrogens of the piperazine molecule are very active, di-substitution generally takes place when piperazine reacts with another reagent. Mono-substitution is difficult because the rate of addition of organic halides to free piperazine is generally slower than their addition to the mono-substituted product first formed.[1] Because of this fact, mono-N-alkylpiperazines cannot be prepared by conventional methods.

There are three general methods of preparing monoalkylpiperazines. First, they may be prepared by treating an excess of piperazine with compounds containing the ethylene oxide linkage. Second, N-monophenylpiperazine may be alkylated and the phenyl group removed. Third, N-monocarbethoxypiperazine may be alkylated and the carbethoxy group removed by hydrolysis.

One of the purposes of this investigation was to develop a satisfactory procedure for the preparation of N-monoalkylpiperazines by the monocarbalkoxy method. N-monocarbethoxylpiperazine was the only member of the series used as an intermediate by previous investigators. It was thought that other N-monocarbalkoxypiperazines might be more easily prepared and converted into N-monoalkylpiperazine.

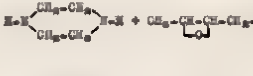
Some new dialkylpiperazines were prepared as intermediates. They were prepared for the purpose of checking like compounds made by reactions in which the end-product could not be predicted.

On account of the high cost of piperazine, various attempts have been made to develop a cheap and convenient synthesis of it or one of its homologs. The synthesis of 2,5-diphenylpiperazine was accomplished. The initial materials for this synthesis are readily available. The phenyl groups on the piperazine nucleus present the possibility of the use of 2,5-diphenyl-piperazine in the synthesis of some homologs of local anesthetics.

REVIEW of the LITERATURE

In 1891, Schmidt and Wichmann[6] treated an excess of piperazine with p-chloronitrobenzene in a sealed tube and obtained N-p-nitrophenylpiperazine.

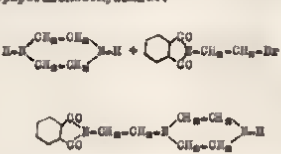
Fourneau and Sarrulet[7] prepared a series of local anesthetics from piperazine. These were mono-derivatives which were prepared by heating an excess of piperazine with compounds containing the ethylene oxide linkage from 3 to 6 hours at 130° to 150° C. According to the authors, piperazine-dimethylcarbinol was synthesized by coupling the oxide of methyl-ethyl-ethylene to piperazine.



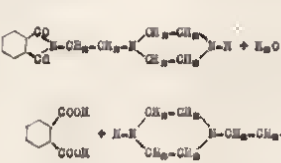
The product might better be called piperazinomethylene-methylethyl carbinol. It is difficult to see how the product could be represented by the formula assigned to it by the authors. The procedure by which mono-substituted piperazines are obtained from ethylene oxides on excess piperazine is covered by a French patent.[8]

Mono-substituted quinoline compounds were

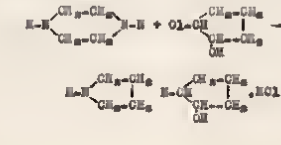
made by Kermack and Smith[8,9] in their attempts to find new anti-malarials by adding 4-chloroquinoline derivatives to an excess of piperazine. They also prepared phthalopiperazinoethylimide:[8]



This was hydrolysed to β-piperazinoethylamine:

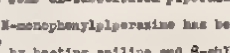


An excess of piperazine and o-chlorohydroxy-



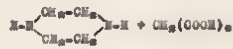
or keto-cycloparaffins yielded mono-compounds for Mousseron[7] and for Godchot and Mousseron.[8] The oxide of indene gave N-β-indenylpiperazine.[9] These authors also noted that some di-substituted piperazine was formed.

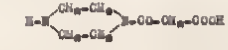
N-monophenylpiperazine has been made by Prelog and Driza[6] by heating aniline and β-chlorodiethylamine hydrochloride:



Pollard and MacDowell[10] succeeded in procuring the same product by refluxing aniline hydrochloride and diethanolamine hydrochloride.

Pollard and Adelson[11] found that anhydrous piperazine hexahydrate reacts, mol for mol, with malonic or diethyl malonic acid, only one imino and one carboxyl group are coupled:

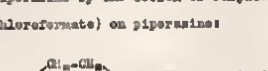




Moore, Boyle, and Thorn[12] were the first to describe a method applicable to the preparation of

monoalkylpiperazines. Monomethylpiperazine is cited in Richter's "Organic Chemistry,"[10] 1925 edition, but no reference is made to the original source of information. There is some doubt whether Richter is referring to 1-methylpiperazine or to 2-methylpiperazine since Prelog and Stepan[10] report the boiling point of N-monomethylpiperazine as 134° to 136° C. while Richter[10] gives 155° C. for the boiling point of the compound listed.

Moore, Boyle and Thore[10] prepared monocarbethoxypiperazine by the action of ethylchlorocarbonate (ethylchloroformate) on piperazine:



Piperazine hexahydrate was dissolved in water to which was added a few drops of an indicator solution with a pH range of 2.8 to 4.8 (brom-phenol blue). Two normal hydrochloric acid was then added until the neutral tint of the indicator appeared. During the course of two and one-half hours, small portions of ethylchloroformate were introduced, the total amount of ethylchloroformate varying from 28 to 32 cc. After each addition the neutral color was brought back by introducing a strong sodium acetate solution.

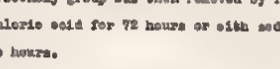
Monobenzoylpiperazine is soluble in ether, while dibenzoylpiperazine is insoluble in ether. Therefore, the reaction was judged complete when a few drops of the reaction mixture was benzoylated and the benzoylation product was completely soluble in ether.

One hundred cc. of 20% sodium hydroxide was added to the reaction mixture, which was ice cooled to diminish the saponification of the esters. The dicarbethoxypiperazine was extracted with ether from the solution three times. The solution was then saturated with potassium carbonate, ice cooled, filtered and exhaustively extracted with ether. From the ethereal solution, dried over anhydrous sodium sulfate, a colorless viscous liquid was obtained, which boiled at 116° to 117° C. at 12 mm. The yield was about 22.2 g. or 70% of theoretical. If the pH limits were maintained by sodium hydroxide instead of sodium acetate, the authors found that the duration of the reaction was lengthened, but that the yields were slightly better.

Moore and his colleagues[15] prepared such N-monopiperazine compounds as the ethyl, β-hydroxyethyl, benzoyl, and p-toluenesulfonyl. N-monopiperazine acetic and N-monopiperazine propionic acids were also synthesized. In all instances they treated monocarbethoxypiperazine with the appropriate derivative. The authors found that monocarbethoxypiperazine could not

be alkylated with ethyl iodide. Ethyl iodide formed a quaternary iodide with the base from which the unchanged monocarbethoxypiperazine could not be separated. The ethyl group was satisfactorily introduced by the use of ethyl-p-toluenesulfonate.

The carbethoxy group was then removed by refluxing with hydrochloric acid for 72 hours or with sodium hydroxide for two hours.



K. A. Jacobi[18] repeated and improved the technique of Moore, Boyle and Thorn.[18] He found that a pH of 2.72 provided conditions for an optimum yield of the mono-derivatives. Jacobi also concluded that the nature of the entering group has an influence on the pH at which mono-substitution occurs, but that the speed of reaction does vary with the reagent used.

Potassium p-benzenesulfonate-azo-benzylaniline was the indicator selected, since it has a pH range of 1.9 to 3.5 with an end point of 2.75. Mono-substituted derivatives were obtained with such reagents as acetyl chloride, acetic anhydride, chloroacetic ester, benzoyl chloride, and p-toluenesulfonyl chloride.

Jacobi's[10] procedure used in the preparation of monocarbethoxypiperazine was somewhat similar to that of Moore and others.[10] Enough N normal hydrochloric acid was added to give a pink color to a water solution containing 5 millimols of piperazine hexahydrate and 2 drops of 0.10% potassium-p-benzenesulfonate-azo-benzylaniline. Sodium acetate was then added until the neutral color of the indicator appeared. Five millimols of ethylchlorocarbonate was slowly added, at room temperature, stirred vigorously after each addition, and the neutral color restored with sodium acetate; then it was allowed to stand for 15 minutes on a water bath to permit the decomposition of the ester. The reaction mixture was then evaporated until an oil remained. This oil was dissolved in 5 ml. of absolute alcohol and the hydrochloride was recrystallized from ether. The yield was 30% of theory and was smaller if sodium hydroxide or sodium carbonate was used instead of sodium acetate. The free base was obtained from the hydrochloride by adding potassium carbonate with ice cooling and was extracted

with ether.

The discrepancies in the two procedures are evident from the following discussion. Jacobi[16] used an indicator with a lower pH range than Moore, Boyle, and Thorn.[18] He reported a lower yield if sodium hydroxide was used to maintain the pH constant. Moore, Boyle, and Thorn[18] stated that the use of sodium hydroxide increased their yield, but lengthened the time of reaction. Their monocarbethoxypiperazine boiled 4° to 6° C. lower than that reported by Jacobi.[16]

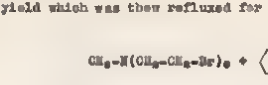
In the process of preparing mono-derivatives by the methods cited above, some of the di-substituted compounds were also formed. Rosdalsky[16] is responsible for reporting 1,4-diethyl-piperazyl diurethane (dicarbethoxypiperazine) as melting at 42° C. and boiling at 215° C. The homologous dicarbomethoxypiperazine was synthesized by Van Dorp,[17] who reported its melting point as 81° C.

Mono-derivatives can also be obtained by another method as was done by Prelog and Stepan.[19] N-methylpiperazine, for example, was prepared by heating di-methyl-bis(β-ethanol)amine with hydrobromic acid for 6 hours in a sealed tube at 180° to 190° C.

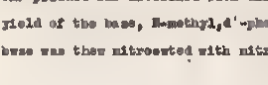
$$CH_3-N(CH_2-CH_2-OH)_2 + 2\ HBr \longrightarrow$$

$$CH_3-N(CH_2-CH_2-Br)_2\cdot HBr + 2\ H_2O$$

N-methyl-bis(β-bromethyl)amine was present in a 65% yield which was then refluxed for 14 hours with aniline,



The product was distilled with alkali to give a 58% yield of the base, N-methyl,4'-phenylpiperazine. The base was then nitrosated with nitrous acid at 2° C:



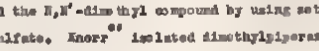
Then it was treated with sulfurous acid, potassium hydroxide, and steam distilled. The hydrochloride of 4-methylpiperazine was obtained with a 74% yield. Distillation with lime yielded the 4-methylpiperazine.

By this method Prelog and Stepan[14] also secured N-ethylpiperazine and N-propylpiperazine dihydrochloride. It can be seen that this route is lengthy and much more involved than the monocarbalkoxy method.

4,N'-dialkylpiperazine compounds are much more readily prepared, and the dimethyl, diethyl, dipropyl,

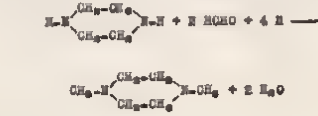
and dibutyl derivatives have been secured by a variety of methods. The use of methyl, ethyl, and propyl halides is patented.[43]

Hahmidt and Wichman[6] prepared these dialkyl-derivatives by the direct union of alkyl halides with piperazine. The ethyl-derivative was also prepared by the use of sodium ethyl sulfate. Ladenburg[45] synthesized the N,N'-dimethyl compound by using methyl potassium sulfate. Knorr[69] isolated dimethylpiperazine after he had heated N-dimethylpiperazine-dimethochloride.



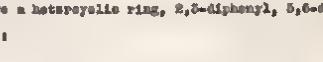
Hofmann[81] found that diethylpiperazine was among the products formed when ethylene bromide was treated with ethylamine.

More recently, N,N'-dimethyl, N,N'-diethyl, and N,N'-dibutylpiperazines have been made by Forsee and Pollard[65] by the condensation of the appropriate aldehyde with piperazine in the presence of a reducing agent.



The addition products with formaldehyde and acetaldehyde were reduced by zinc and hydrochloric acid while formic acid was used with butyraldehyde.

In investigating the possibilities of synthesizing a new homolog of piperazine, it was discovered that Mason[88] in 1897 had reacted benzil with ethylene diamine. This gave a heterocyclic ring, 2,3-diphenyl, 5,6-dihydropyrazine:



The condensation product of a primary amine with a carbonyl group, water being eliminated, is known as a Schiff's base.[84] The above compound would then be a di-Schiff's base as there are two double bond linkages between the carbon and nitrogen atoms.

The reduction of Schiff's bases has been attempted in various manners. A German patent[85] covers the electrolytic reduction in acid solution. A Hand call of the type described by Luken[86] gave a poor yield when used on methylene-p-aminophenol.[87] Hydrogenation in alcohol in the presence of palladium is also covered by a patent.[88] Wagner[89] reduced methylene-p-aminophenol satisfactorily by running it into 60% sulfuric acid and

adding a quantity of zinc dust equivalent to the weight of the base being used.

Benzylidene aniline has been hydrogenated by Mailhe[22] to phenylbenzyl amine at 220° to 230° C. in the presence of finely divided nickel. However, our laboratory lacked the equipment necessary to carry out this reduction successfully.

It has been noted generally by observers that Schiff's bases are sensitive to acids, being resolved into their constituents by strong hydrochloric acid.[23] Therefore, the reduction of 2,3-diphenyl-dihydropyrazine was attempted in alkaline solution and was accomplished by the action of sodium hydroxide and zinc.

DISCUSSION

N-mono-derivatives of piperazine cannot be successfully prepared under the conditions that generally prevail when an acidic group or alkyl halide reacts with an alkyl diamine. Prior to the use of chlorocarbonates by Moore, Doyle, and Thorn,[10] the conventional method of preparing N-mono-substituted compounds was to use from 3 to 5 mols of piperazine in excess to the other reagent. However, an excess of piperazine did not prevent the formation of some of the di-substituted derivatives.[9]

One of the objectives of this investigation was to ascertain if the use of N-monocarbethoxy piperazine as an intermediate was preferable to the use of other N-monocarbalkoxy piperazines in the preparation of monoalkylpiperazines. The symmetric of these intermediates was accomplished by the use of methyl, ethyl, propyl, and amylchlorocarbonates. The monocarbobutoxypiperazine could not be separated from the corresponding di-derivative.

The miscibility of the chlorocarbonates with water decreases with an increase in the molecular weights. Likewise, the speed of the reaction decreases as the molecular weights increase.

N-monocarbomethoxypiperazine can be prepared more rapidly, without sacrificing the yield, than any

other member of the series. The amount of N,N'-dicarbethoxypiperazine formed as a by-product is negligible and it can be readily separated from the mono-derivative by vacuum distillation.

The synthesis of N-monocarbopropoxypiperazine differs little from the preparation of N-monocarbethoxypiperazine except that the reaction is slightly slower.

Butylchlorocarbonate reacts very slowly with piperazine in water solution. The time needed for the completion of the reaction makes its preparation impracticable. The reaction can be accelerated if 50% alcohol is used as the solvent. However, it is difficult to control the pH of the alcoholic solution by colorimetric methods. Both the mono and the di-derivatives were formed and it was impossible to satisfactorily remove the N,N'-dicarbobutoxypiperazine from the mono-compound.

There are conflicting reports in the literature regarding the effect of sodium hydroxide on the yield of N-monocarbethoxypiperazine. This compound was prepared by maintaining the pH constant by means of sodium hydroxide instead of sodium acetate. The yield was approximately 40% less than in the procedure in which sodium acetate was used. A smaller yield was obtained when bromophenol blue, pH range of 3.0 to 4.6, was used. The use of potassium benzenesulfonate-aza-

benzylaniline instead of bromophenol blue substantiates Jacobi's[16] contention that better results are obtained at a lower pH.

It is difficult and tedious to maintain a standard color by the addition of sodium acetate. Monoacarbalkoxypiperazine could be more readily prepared if the pH of the solution could be automatically controlled. This difficulty could be overcome if a reagent that had a large buffer capacity at a pH of 8.7d could be introduced in the piperazine solution. Since there is no available data on buffer capacities, an electrometric determination of the capacity of a saturated solution of potassium acid phthalate was made. Potassium acid phthalate was selected because it is used in the Clark and Lubs set of standard buffers and its presence in the reaction mixture is not objectable.

An approximately saturated solution, containing 9.77d0 g. per 2d cc. of potassium acid phthalate, was electrometrically titrated at 25° C. against 0.1 normal hydrochloric acid.

Quinhydrone Electrode vs Saturated Calomel Electrode

CC. of 0.1 N HCl	E. M. F. (Millivolts)	pH
0.0	0.3325	3.66
20.12	0.2492	2.49
34.84	0.2327	2.86
40.16	0.2096	2.06
49.84	0.1782	1.92
22.84	0.2362	2.72
70.08	0.2249	2.64
79.79	0.2015	2.65
23.65	0.2186	2.51
118.84	0.3230	2.09

From this data it can be seen that if the amount of 0.1 N HCl is less than 86 cc., the pH will exceed 2.8. If more than 86 cc. of 0.1 N acid is present, the pH will drop below 2.7. Therefore, the amount of HCl present at any time must not vary more than the amount equivalent to 2 cc. of 0.1 N HCl or the pH range of 2.70 to 2.80 will be exceeded. It would be more difficult to keep the amount of HCl within this range than to keep the color constant by means of a sodium acetate solution.

Moore, Boyle, and Thorn[16] determined the completion of the reaction, in the synthesis of N-monocarb-

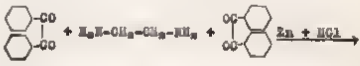
ethoxypiperazine, by benzoylating a few drops of the reaction mixture. Since dibenzoylpiperazine is insoluble in ether, ethylchlorocarbonate was added until the benzoylation product was completely soluble in ether. The results of the present work leave some doubt as to the advisability of using this test.

The procedure for the preparation of N-monocarbalkoxypiperazine used in this investigation involves modifications of that used by Jacobi[18] and by Moore, Boyle, and Thorn.[18] Experimental evidence shows that these modifications tend to make this procedure superior to that of the above authors.

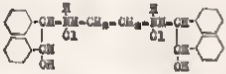
Some new N,N'-dialkylpiperazines were prepared and their constants determined. These constants were to be used to check against the constants of similar products made by other methods. A comparison of the N-monoalkyl-derivative with the corresponding N,N'-dialkyl-derivative showed that the boiling point of N-mono-n-butylpiperazine was lower than that of N,N'-di-n-butylpiperazine. The boiling point of N-monoisobutylpiperazine is higher than that of N,N'-diisobutylpiperazine.

N,N-diphenylpiperazine was synthesized by the reduction of the product formed by the condensation of ethylenediamine with benzil. This condensation product was successfully reduced by the use of zinc and sodium hydroxide.

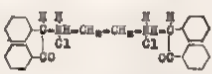
N,N'-bis(1,2-diphenyl,2-hydroxyethyl)ethylene-diamine dihydrochloride was formed by the use of zinc and hydrochloric acid. Analysis for nitrogen would not prove whether the product had the structure represented by A or B.



(A)

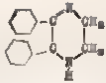


(B)

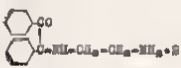


The validity of the structure assigned was proven by substituting benzoin for benzil in the reaction, above. Benzoin could give only the compound represented by (A). A mixed melting point proved that the product formed from benzoin was identical with that formed from benzil.

A product melting at 120° to 121° C. was obtained when aluminum and sodium hydroxide was used as the reducing agent. Analysis for nitrogen indicated a structure represented by the following:



If this were true, boiling hydrochloric acid should form a compound of this type:



The melting point of a mixture composed of the compound melting at 180° to 181° C. and the compound treated with hydrochloric acid indicated that the hot hydrochloric acid had neither hydrolyzed the substance nor formed an addition product with it. The product melting at 180° to 181° C. could not be reduced with zinc and sodium hydroxide, so no structure has been assigned to it.

The reduction of the 2,3-diphenyl dihydropyrazine was also attempted by means of formic acid and by the action of sodium on alcohol. Neither method was successful.

The methods of preparation and the physical constants of the compounds discussed will be found in the experimental part of this dissertation.

EXPERIMENTAL

EXPLANATION

The preparation of reagents and limitation of terms used are given below:

SODIUM ACETATE SOLUTION. One hundred and twenty-five grams of sodium acetate was dissolved in 100 cc. of water and the solution was then filtered. Crystals of sodium acetate had a tendency to separate out of a more concentrated solution.

STOCK SOLUTION OF POTASSIUM ACID PHTHALATE.[21] This was a fifth molar solution consisting of 10.279 g. of potassium acid phthalate per 250 cc. of solution. The potassium acid phthalate crystals had been dried over night at 105° C.

BUFFER OF pH 2.75.[21] Fifty cc. of the stock solution of potassium acid phthalate and 56.12 cc. of 0.1000 normal hydrochloric acid were diluted to 200.0 cc. The pH of this buffer was determined by an electrometric measurement. The reading of the quinhydrone electrode at 30° C. was 0.2875 millivolt; this corresponds to a pH of 2.76.

BUFFER OF pH 3.00.[21] Fifty cc. of the stock solution of potassium acid phthalate and 40.64 cc. of 0.1000 normal hydrochloric acid were diluted to 200.0 cc.

SODIUM BENZENESULFONATE-AZO-BENZYLANILINE INDICATOR SOLUTION. Four-tenths gram of benzenesulfonic acid azo-benzylaniline was triturated with 15 cc. of 0.1000 normal sodium hydroxide. This was diluted to a volume of 100 cc., making a 0.4% solution.

The term, NEUTRAL POINT or NEUTRAL COLOR, refers to the pH at which the acidic and basic forms of the indicator are in equilibrium. When sodium benzenesulfonate-azo-benzylaniline exists as a base (pH of 1.9) it is yellow and changes to red upon becoming an acid (pH of 3.3).

All BOILING POINTS and MELTING POINTS recorded in this work were taken with a calibrated thermometer. The thermometer used in taking the temperature of the oil bath during vacuum distillations was not calibrated. Pressure values, in millimeters, were read from a standard laboratory manometer that had not been calibrated in any way.

All ANALYSES were made for nitrogen by the standard Kjeldahl method.

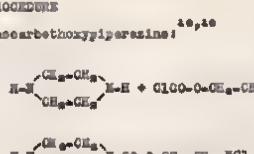
In some instances more than one SOLVENT was used in the purification process. The first solvent listed in the table of properties was preferable in most cases.

The values for the ATOMIC WEIGHTS were taken from the 1933 Revision of International Atomic Weights.[88]

EXPERIMENTAL

PROCEDURE

1. N-monocarbethoxypiperazine:[10,16]



Thirty grams of piperazine hexahydrate was dissolved in 30 cc. of water, and 10 drops of sodium p-benzenesulfonate-azo-benzylaniline indicator solution was added. Approximately 28 cc. of concentrated hydrochloric acid was added, with ice cooling, before the indicator changed to a color indicating a pH of 8.75. This color was determined by a comparison with a test-tube containing an indicator and the buffer of pH 8.75. If too much hydrochloric acid was added, the neutral point was brought back by the addition of the sodium acetate solution from a burette.

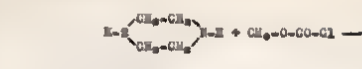
Sixteen and two-tenths cc., 1.2 cc. in excess of the calculated quantity, of ethylchlorocarbonate was added, drop by drop, from another burette. After each addition, the neutral color of the indicator was re-

stored with sodium acetate solution. Approximately 25 cc. of sodium acetate was needed to keep the pH constant. The reaction was carried out at 15° C. About 45 minutes were consumed during the reaction between the ester and the piperazine. Throughout the reaction the ratio of 1 drop of indicator to 10 cc. of solution was maintained.

The reaction mixture was treated with 75 cc. of 50% NaOH, cooled, and then was extracted with ether to remove the diearbethoxypiperazine. The solution was then saturated with potassium carbonate, filtered, and exhaustively extracted with ether. The ether extracts were dried over night with anhydrous sodium sulfate or with Drierite, filtered, and concentrated. Each extraction product was then vacuum distilled. The yield was 14.7 g., corresponding to 82% of theory. The mono-derivative was a viscous colorless liquid soluble in water and common organic solvents.

The boiling point of the diearbethoxypiperazine was 167° to 169° C. at 11 mm. and oil both at 210° to 215° C. It was more viscous than the mono-compound and solidified in a water cooled condenser. It became a white crystalline mass upon standing at room temperature from 1 to 4 days. The literature[18] states that diearbethoxypiperazine melts at 42° C.

2. 2-monocarbomethoxypiperazine.



Thirty-eight grams of piperazine ase dissolved in 50 ac. of ester cactaining 12 drops of the indicator solution. The acid color of the indicator was brought about by the addition of approximately 27 cc. of concentrated hydrochloric acid.

The solution was kept at 15° C. during the addition of 17 cc., 1.2 cc. in excess of the calculated quantity, of methylchlorocarbonate. The solution was vigorously stirred while adding the ester, drop by drop. The neutral color of the indicator, pH. of 2.72, ase maintained by the addition of 70 to 80 cc. of sodium acetate solution. The color of the reaction mixture was compared with a test-tube containing 20 cc. of the buffer of pH 2.75 and 2 drops of the indicator. About 35 minutes elapsed during the reaction of the ester with the piperazine.

The solution was then treated with 72 cc. of 20% NaOH, with ice cooling, and extracted with ether. After ecturating with potassium carbonate and filtering

off the excess, the solution was again extracted with ether. The ethereal solutions were dried with anhydrous sodium or calcium sulfate. The ether was allowed to evaporate and the residual liquid vacuum distilled.

Almost all of the product extracted before saturation with potassium carbonate, proved to be N-monocarbomethoxypiperazine. A few crystals of dicarbethoxypiperazine were deposited in the condenser but not enough to warrant purification.

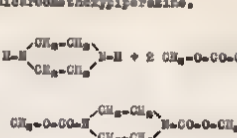
The N-monocarbomethoxypiperazine was further dried with anhydrous sodium carbonate and analyzed. The samples were weighed out in small, short-necked ampoules with a volume of about 1 cc. These ampoules were filled by means of a hypodermic syringe.

(E) N-monocarbomethoxypiperazine.

Structural Formula

Empirical Formula	$C_6H_{12}N_2O_2$
Molecular Weight	144.110
Boiling Point	98°-99° C. at 7 mm. Oil bath 140° C.
Theoretical Yield	14.4
Actual Yield	7.4
Percentage Yield	51
Percentage of Nitrogen, Theory	19.44
Percentage of Nitrogen, Found	19.38
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

3. 3,3'-dicarbomethoxypiperazine.[17]



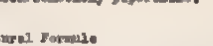
A sufficient quantity of 3,3'-dicarbomethoxypiperazine could not be obtained as a by-product in the preceding reaction to study its properties. It had been previously synthesized by Von Dorp,[17] but the Recueil des Travaux Chimiques des Pays-Bas is not available.

Ten grams of piperazine hexahydrate was treated with 9 cc. of methylchlorocarbonate. The reaction was rapid and exothermic. At the conclusion of the reaction, the white crystals were dried on a Buchner funnel.

A small portion was recrystallized from methyl alcohol, but petroleum ether gave crystals with a higher melting point. Further experimentation showed that hexane was the best recrystallizing medium.

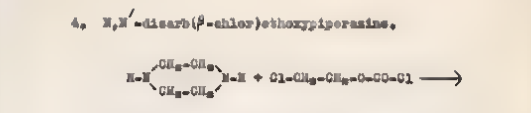
(3) N,N'-dicarbomethoxy piperazine.[17]

Structural Formula



Empirical Formula	$C_6H_{12}N_2O_4$
Molecular Weight	203.125
Melting Point	82.5°-83.5° C.
Melting Point[17]	81° C.
Theoretical Yield	10.4 g.
Actual Yield	8.5 g.
Percentage Yield	81
Percentage of Nitrogen, Theory	13.87
Percentage of Nitrogen, Found	13.88
Recrystallized from	Hexane or petroleum ether
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

4. N,N′-dicarb(β-chlor)ethoxypiperazine.



An attempt was made to prepare N-monocarb(β-chlor)ethoxypiperazine by a method analogous to that used in the preparation of N-monocarbethoxypiperazine. The product was extracted by means of ether and chloroform. White crystals separated out after the extracts had been left standing for 48 hours. These crystals melted from 110° to 115° C.

The ether and chloroform extracts were concentrated and combined. Vacuum distillation was attempted, but a viscous brown mass remained after the solvent had evaporated. This brown substance could not be purified and was thought to consist largely of the decomposed di-derivative.

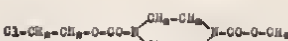
N,N′-dicarb(β-chlor)ethoxypiperazine was made as follows: 15 g. of sodium carbonate, dissolved in a minimum quantity of water, was mixed with 19.4 g. of piperazine hexahydrate dissolved in a minimum amount of alcohol. The mixture was placed in an ice bath and 21 cc. of β-chlorethylchlorocarbonate was added. The reaction was rapid and accompanied by much foaming.

After cooling, the white granular precipitate was filtered off and air dried.

The product is soluble in dioxane, ethylene chloride, and chloroform. It was dried in a vacuum desiccator for three days before an analysis was made.

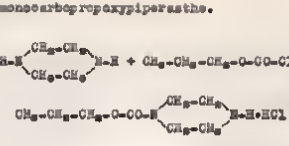
(4) N,N'-dicarb(β-chlor)ethoxypiperazine.

Structural Formula



Empirical Formula	$C_{12}H_{18}N_2O_4Cl_2$
Molecular Weight	301.06
Melting Point	117°-117.5° C.
Theoretical Yield	50.1 g.
Actual Yield	50.4 g.
Percentage Yield	99
Percentage of Nitrogen, Theory	9.07
Percentage of Nitrogen, Found	9.07
Recrystallized from	Toluene or butyl cellosolve
Solubility in Water	Slightly soluble, Hot
Solubility in Alcohol	Soluble
Solubility in Ether	Slightly soluble

5. N-monocarbopropoxypiperazine.



Thirty-eight and eight-tenths grams of piperazine was dissolved in 50 cc. of water containing 10 drops of sodium hexadecylsulfonate-azo-benzylaniline. Thirty-seven cc. of concentrated hydrochloric acid was necessary to neutralize the piperazine.

Twenty-five cc., 2.5 cc. in excess of the calculated quantity, of propylchlorocarbonate was slowly added with vigorous stirring. The indicator was kept at its neutral point by the addition of sodium acetate solution. The reaction mixture was kept at 50° C. since the chlorocarbonate is not readily soluble in cold water. The reaction required 55 minutes for its completion.

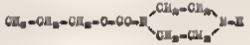
The solution was made alkaline by the addition of 50 cc. of 50% sodium hydroxide and the product was extracted with ether. Then the ethereal solution was saturated with potassium carbonate, filtered, and further extracted. Upon evaporation of the ether, after drying,

it was found that about 90% of the product had been extracted before the addition of the potassium carbonate.

The product was vacuum distilled, dried with Drierite, and redistilled. The samples for analysis were weighed out in ampoules.

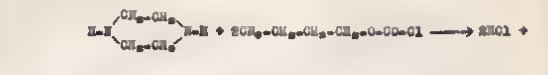
(8) N-monocarbopropoxypiperazine.

Structural Formula



Empirical Formula	$C_8H_{16}N_2O_2$
Molecular Weight	172.141
Boiling Point	120.4°-121.5° C. at 5.76 mm. Oil bath 175° C.
Theoretical Yield	34.4 g.
Actual Yield	26 g.
Percentage Yield	75
Percentage of Nitrogen, Theory	16.28
Percentage of Nitrogen, Found	16.36
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

4. N,N'-dicarbobutoxypiperazine.



Ten grams of piperazine ase dissolved in 25 cc. of a 33% solution of sodium carbonate. Thirteen grams of butylchlorocarbonate was added, the contents of the flask warmed and agitated. White crystals were formed in the mixture after the flask had stood over night in the ice-box.

The crystals were purified, dried in a vacuum desiccator in the presence of paraffin for 4 days and analyzed.

The preparation of N-monocarbobutoxypiperazine was attempted by a method analogous to that used for the synthesis of N-monopropoxypiperazine. Butylchlorocarbonate is almost immiscible in water and for that reason the piperazine solution was kept at 60° C. It took about two and one-half hours to complete the reaction.

The ether extracts appeared to be similar, so they were combined and vacuum distillation was attempted. After the ether had evaporated, a white crystalline mass remained in the distilling flask, which substance became

a viscous liquid upon standing.

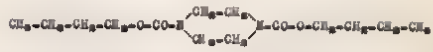
This liquid was distilled at atmospheric pressure from a side-arm distilling flask. The boiling point ranged from 230° to 310° C. It became a semi-solid upon cooling, and was soluble in all common organic solvents.

Another attempt was made using 50% alcohol as the reaction medium. The color of the reaction mixture was compared with the color of a solution containing 10 cc. of buffer of pH 8.75, 10 cc. of alcohol, and 4 drops of indicator.

A water-cooled condenser could not be used during the vacuum distillation of the product; even an air-cooled condenser became clogged. The distillate, which became a gel upon cooling, was redistilled, but remained a gel. Analysis of various fractions indicated it to be a mixture of N-mono and N,N'-dicarbobutoxy-piperazine.

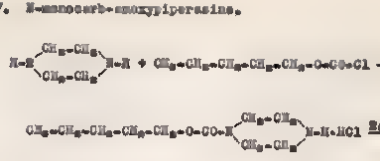
(5) 5,5'-dicarbobutoxypiperazine.

Structural Formula



Empirical Formula	$C_{14}H_{26}N_2O_4$
Molecular Weight	285.215
Melting Point	43°-44° C.
Theoretical Yield	14.7 g.
Actual Yield	12.5 g.
Percentage Yield	85
Percentage of Nitrogen, Theory	9.79
Percentage of Nitrogen, Found	9.25
Recrystallized from	Petroleum ether or hexane
Solubility in Water	Insoluble, cold Forms an oil, hot
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

7. N-monocarbo-amoxypiperazine.



Thirty grams of piperazine hexahydrate was dissolved in 27 cc. of concentrated hydrochloric acid. One hundred cc. of 50% alcohol containing 15 drops of indicator was added.

The neutral color of the indicator was brought back with a sodium acetate solution. The neutral color was determined by a comparison with a solution containing 10 cc. of buffer of pH 2.76, 10 cc. of alcohol, and 2 drops of indicator.

The solution was heated to a temperature between 70° and 80° C., and 24 cc. of amylchlorocarbonate was slowly added with the subsequent additions of sodium acetate. About 60 minutes were required for the reaction.

The mixture was extracted with ether after being made alkaline with sodium hydroxide. The solution was then saturated with anhydrous potassium carbonate and the extraction procedure repeated. It was noted that there

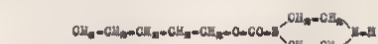
was more N-monocarb-amoxypiperazine in the second extract than in the first.

The first extract was placed in a vacuum distillation apparatus and the oil bath was kept at 110° C. until white crystals were no longer deposited in the condenser. After the condenser had been cleaned, the distillation was resumed. The same procedure was used on the product of the second extract; the distillates were combined, redistilled, and analyzed.

This synthesis of N-monocarb-amoxypiperazine was attempted in aqueous solution. The ethylchlorocarbonate appeared to be entirely immiscible with water at 30° C. and only slightly miscible with water at 80° C. The reaction proceeded so slowly that an appreciable quantity of the mono-compound could not be isolated.

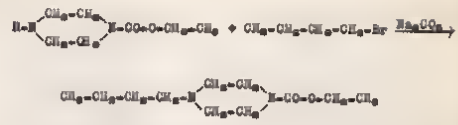
(7) N-monocarb-oxypiperazine.

Structural Formula



Empirical Formula	$C_{12}H_{24}N_2O_2$
Molecular Weight	200.17
Boiling Point	141°-142° C. at 6 mm. Oil bath 150°-155° C.
Theoretical Yield	31 g.
Actual Yield	9.5 g.
Percentage Yield	30
Percentage of Nitrogen, Theory	14.00
Percentage of Nitrogen, Found	14.18
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

d. N-n-butyl, N'-ethylpiperazine-carboxylate.



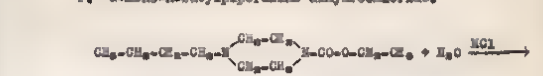
Fifteen and eight-tenths grams of N-monocarbethoxypiperazine was added to a concentrated solution of sodium carbonate (8 g. dissolved in 25 cc. of water). Seventeen grams of n-butyl bromide was introduced and the resulting mixture was refluxed for 5 hours. After being made strongly alkaline with 30% sodium hydroxide, the solution was exhaustively extracted with ether. The ethereal extract was dried over potassium carbonate, filtered, concentrated, and vacuum distilled twice. The distillate was further dried over anhydrous potassium carbonate, filtered in a desiccator, and analyzed.

(d) N-n-butyl, N'-ethylpiperazine-carbexylate.

Structural Formula

Empirical Formula	$C_{11}H_{22}N_2O_2$
Molecular Weight	214.188
Boiling Point	143°-145° C. at 8 mm. Oil bath 195° C.
Theoretical Yield	31.4 g.
Actual Yield	18 g.
Percentage Yield	84
Percentage of Nitrogen, Theory	13.08
Percentage of Nitrogen, Found	13.05
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

P. N-mono-n-butylpiperazine dihydrochloride.



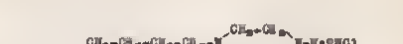
Seventeen and two-tenths grams of N-n-butyl, N'-ethylpiperazinecarboxylate were refluxed with 80 cc. of concentrated hydrochloric acid for 50 hours. The apparatus was shaken by means of a mechanical vibrator. The excess acid and water was distilled off at the conclusion of the hydrolysis.

A white crystalline mass remained, which was crystallized 4 times, alternately, with absolute alcohol and butanol. The crystals were dried for 36 hours at 140° to 150° C. and analyzed. The results of the analysis were low. Inspection showed that the hydrochloride was exceedingly hygroscopic. Samples were placed in small weighing bottles which were dried at 140° to 150° C, for 7 days. Even then there was still a minute loss of weight during a 12 hour period.

During this dehydration the crystals turned from a white to a yellowish brown color. The weighing bottle and sample were weighed, about 0.3 g. poured into a Kjeldahl flask, the bottle quickly re-stoppered, and weighed.

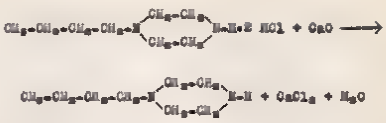
(9) N-mono-n-butylpiperazine dihydrochloride.

Structural Formula



Empirical Formula	$C_8H_{20}N_2Cl_2$
Molecular Weight	215.086
Melting Point	242°-244° C. (dec)
Theoretical Yield	17.3 g.
Actual Yield	15.2 g.
Percentage Yield	88
Percentage of Nitrogen, Theory	13.03
Percentage of Nitrogen, Found	13.05
Recrystallized from	Butanol or absolute alcohol
Solubility in Water	Soluble
Solubility in Alcohol	Slightly Soluble
Solubility in Ether	Insoluble

10. N-mono-n-butylpiperazine.

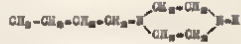


Seven grams of CaO was thoroughly mixed with 10.4 g. of N-mono-n-butylpiperazine dihydrochloride. Because of the hygroscopic nature of the piperazine derivative, it was difficult to prevent a loss of the mixture by adherence to the containers used in its handling.

The crude mixture was distilled in vacuo. The distillate was again distilled, dried, redistilled, and analyzed.

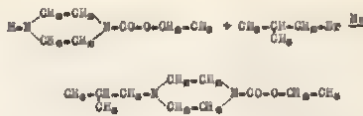
(10) N-mono-n-butylpiperazine.

Structural Formula



Empirical Formula	$C_8H_{18}N_2$
Molecular Weight	142.156
Boiling Point	74°-76° C. at 15 mm. Oil bath 120° C.
Theoretical Yield	8.9 g.
Actual Yield	4.5 g.
Percentage Yield	55
Percentage of Nitrogen, Theory	19.69
Percentage of Nitrogen, Found	19.55
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

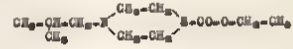
11. N-isobutyl,N'-ethylpiperazine-carboxylate.



Fifteen grams of N-monocarbethoxypiperazine was placed in a round-bottom flask containing 17 g. of isobutyl bromide and 8 g. of sodium carbonate dissolved in 25 cm. of water. The mixture was refluxed over night, after which it was thoroughly extracted with chloroform, dried, and distilled. The product was further dried by means of anhydrous sodium carbonate, distilled, and redistilled.

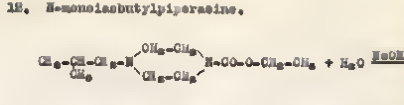
(11) N-isobutyl, N'-ethylpiperazine-carboxylate.

Structural Formula



Empirical Formula	$C_{11}H_{22}N_2O_2$
Molecular Weight	214.188
Boiling Point	123.5°-125.5° C. at 4.5 mm. Oil bath 155° C.
Theoretical Yield	20.5 g.
Actual Yield	14.4 g.
Percentage Yield	66
Percentage of Nitrogen, Theory	14.08
Percentage of Nitrogen, Found	13.97
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

18. N-monoisobutylpiperazine.



Ten and two-tenths grams of N-isobutyl,N'-ethylpiperazine-carboxylate was refluxed with 10 g. of a 50% sodium hydroxide solution for 5 hours. The reaction mixture was then vacuum distilled. The monoisobutylpiperazine was separated from the water in the distillate by extraction with chloroform. The chloroform extract was thoroughly dried over anhydrous potassium carbonate and distilled. The product was distilled two more times and analyzed.

Concentrated hydrochloric acid was added to 6.5 g. of N-monoisobutylpiperazine, and the precipitate was dissolved in absolute alcohol. The solution was chilled and filtered. More acid was added to the filtrate to ascertain if all of the free base had been converted to the hydrochloride. After being recrystallized three times from butanol, it was found that the melting point was 282° to 283.5° C.

The dihydrochloride was dried for 3 hours at 150° C. and overnight in a desiccator before being

weighed out for analysis. The samples were then dried for 15 hours at 140° C. and re-weighed. Each sample had lost about one-third of its weight. Analysis of these compounds, without further drying, indicated about 11.8% of nitrogen. The theoretical percentage of nitrogen is 13.03.

(12) N-monoisobutylpiperazine.

Structural Formula

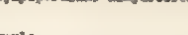
Empirical Formula	$C_8H_{18}N_2$
Molecular Weight	142.156
Boiling Point	151°-152.5° C. at 5 mm. Oil bath 170° C.
Theoretical Yield	5.76 g.
Actual Yield	5.0 g.
Percentage Yield	75
Percentage of Nitrogen, Theory	19.59
Percentage of Nitrogen, Found	19.46
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

15. N,N'-diisopropylpiperazine dihydrobromide.

Twenty-seven cc. of isopropyl bromide was added to 50 cc. of a solution containing 19.4 g. of piperazine hexahydrate and 15 g. of sodium carbonate. The mixture was refluxed for 5 hours, made strongly alkaline with 20 cc. of 50% sodium hydroxide, and extracted with chloroform. The chloroform was distilled off and the distillation of the free base attempted. It showed signs of decomposition so an excess of 40% hydrobromic acid was added. The excess acid and water was removed by distillation and the resulting product recrystallized twice from butanol and twice from absolute alcohol. An analysis was made after drying for 26 hours at 140° C.

(18) N,N'-diisopropylpiperazine dihydrobromide.

Structural Formula



Empirical Formula	$C_{10}H_{24}N_2Br_2$
Molecular Weight	332.035
Melting Point	268°-271° C. (dec.)
Theoretical Yield	53.2 g.
Actual Yield	11.8 g.
Percentage Yield	38
Percentage of Nitrogen, Theory	8.44
Percentage of Nitrogen, Found	8.34
Recrystallised from	Butanol or Absolute alcohol
Solubility in Water	Soluble
Solubility in Alcohol	Slightly soluble
Solubility in Ether	Insoluble

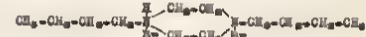
14. N,N'-di-n-butylpiperazine dihydrobromide

Nine and seven-tenths grams of piperazine hexahydrate was refluxed for one hour with 15 cc. of n-butyl bromide. The excess bromide and water was distilled off. When the temperature reached 135° C. the residue in the distilling flask solidified.

The residual crystalline mass was dissolved in hot absolute alcohol. White crystals appeared upon cooling. The product was recrystallized three additional times, dried for 24 hours at 110° to 120° C., and analyzed.

(14) N,N'-di-n-butylpiperazine dihydrobromide.

Structural Formula



Empirical Formula	$C_{12}H_{28}N_2Br_2$
Molecular Weight	360.07
Melting Point	208.6°-208.8° C. (dec.)
Theoretical Yield	14 g.
Actual Yield	5.5 g.
Percentage Yield	21
Percentage of Nitrogen, Theory	7.78
Percentage of Nitrogen, Found	7.97
Recrystallized from	Absolute alcohol
Solubility in Water	Soluble
Solubility in Alcohol	Slightly soluble
Solubility in Ether	Insoluble

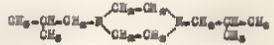
15. N,N'-diisobutylpiperazine.

Twenty-three cc. of isobutyl bromide was refluxed for 5 hours with a solution containing 15.4 g. of piperazine hexahydrate, 15 g. of sodium carbonate, and 50 cc. of water. The reaction mixture was extracted with ether. The ethereal solution was dried with anhydrous potassium carbonate and the excess ether evaporated.

The residual liquid was placed in the distillation flask and the pressure of the system was reduced; the temperature of the oil bath was slowly raised. Crystals appeared in the condenser until the oil bath reached 110° C. The crystals were removed from the condenser and the distillation resumed. The distillate was dried, redistilled, and analyzed.

(16) 5,8'-diisobutylpiperazine.

Structural Formula



Empirical Formula	$C_{12}H_{26}N_2$
Molecular Weight	198.219
Boiling Point	98°-99° C. at 4 mm. Oil bath 165° C.
Theoretical Yield	10.8 g.
Actual Yield	4 g.
Percentage Yield	20
Percentage of Nitrogen, Theory	14.14
Percentage of Nitrogen, Found	14.06
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

19. N,N'-di-ter-butylpiperazine.

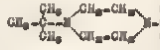
A mixture of 9.7 g. of piperazine hexahydrate and 15 cc. of ter-butyl bromide was refluxed for one hour. The reaction was then fractionated.

At 126° C. crystals appeared in the condenser, so the distillation was discontinued. The residue in the distilling flask solidified as did the fraction boiling between 117° and 125° C. The solids were combined and recrystallized two times from butanol; the same procedure was then carried out using absolute ethanol.

The product was dried over night at 110° C. and was allowed to stand in a vacuum desiccator for one week. It analyzed as the free base and not as the expected hydrobromide. Evidently the hydrobromide of tertiary amines, in which one of the alkyl groups contains a tertiary carbon atom in close proximity to the nitrogen atom, is unstable.

(16) N,N'-di-ter-butylpiperazine.

Structural Formula



Empirical Formula	$C_{12}H_{26}N_2$
Molecular Weight	198.219
Melting Point	207.7°-208.8° C.
Theoretical Yield	8.9 g.
Actual Yield	8.1 g.
Percentage Yield	9%
Percentage of Nitrogen, Theory	14.14
Percentage of Nitrogen, Found	14.09
Recrystallized from	Butanol or ethanol
Solubility in Water	Soluble
Solubility in Alcohol	Slightly soluble
Solubility in Ether	Insoluble

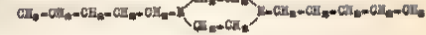
17. N,N'-di-n-amylpiperazine.

Twenty-seven cc. of n-amyl bromide was refluxed for 5 hours with a solution containing 19.4 g. of piperazine hexahydrate and 15 g. of sodium carbonate. At the conclusion of the refluxing the di-substituted piperazine was extracted with ether.

The ethereal solution was dried by means of anhydrous potassium carbonate, and vacuum distilled. The product decomposed if distilled at atmospheric pressure. After further drying, the liquid was redistilled and analyzed.

(LV) N,N'-di-n-amylpiperazine.

Structural Formula



Empirical Formula	$C_{14}H_{30}N_2$
Molecular Weight	226.25
Boiling Point	140°-141° C. at 6 mm. Oil bath 160° C.
Theoretical Yield	25.6 g.
Actual Yield	12.4 g.
Percentage Yield	25
Percentage of Nitrogen, Theory	12.38
Percentage of Nitrogen, Found	12.26
Solubility in Water	Soluble
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

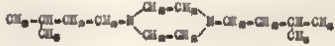
18. N,N'-diisoamylpiperazine dihydrobromide.

Nine and seven-tenths grams of piperazine was dissolved in 25 cc. of water and mixed with a solution containing 25 g. of sodium carbonate. Fourteen cc. of isoamyl bromide was added to the mixture, which was refluxed for 4 hours.

Distillation of the product was attempted at atmospheric pressure, but decomposition resulted. The residue was dissolved in absolute alcohol, filtered, and made strongly acidic with concentrated hydrochloric acid. The alcoholic solution was distilled and the white solid that remained was recrystallized two times from both butanol and absolute ethanol. The product was dried for 25 hours at 120° C. before it was analyzed. It darkened slightly during the drying process.

(13) N,N'-dibenzylpiperazine dihydrobromide.

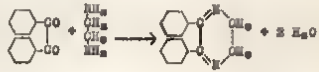
Structural Formula



Empirical Formula	$C_{18}H_{24}N_2Br_2$
Molecular Weight	388.098
Melting Point	319°-321° C. (Sec.)
Theoretical Yield	19.4 g.
Actual Yield	4.2 g.
Percentage Yield	88
Recrystallized from	Butanol or absolute alcohol
Solubility in Water	Soluble
Solubility in Alcohol	Slightly soluble
Solubility in Ether	Insoluble

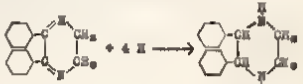
16. 2,3-diphenylpiperazine.

Twenty-one grams of benzil was dissolved in hot alcohol and 10 g. of 85% ethylenediamine added through the reflux condenser. The mixture was refluxed for 1 hour although the reaction appeared to be complete after the first 20 or 30 minutes.



The golden yellow crystals were filtered, dried, and recrystallized from alcohol. Upon being recrystallized from hexane, the crystals melted at 161.6° to 162.5° C. Mason[22] reports the melting point to be 160° to 161° C.

Ten grams of the 2,3-diphenyl-dihydropyrazine was dissolved in 100 cc. of absolute alcohol. Eighteen grams of sodium hydroxide, dissolved in 30 cc. of water, was added to the hot alcohol solution. The hot solution was mechanically stirred while 10 g. of zinc powder was introduced in the course of two hours.



The temperature of 50° to 60° C. was maintained for 5 hours, after which the mixture was allowed to cool to room temperature. It was stirred for an additional 5 hours. The volume was kept constant during the heating by the addition of absolute alcohol.

The unused zinc was filtered off and the volume of the filtrate reduced to approximately 75 cc. Yellowish white crystals separated out upon cooling. These were purified and dried in a vacuum desiccator before being analyzed.

If powdered aluminum is substituted for zinc, a product differing from the above is obtained. It has a light canary yellow color and melts at 120° to 121° C., while 2,3-diphenylpiperazine melts at 105.5° to 106.5° C. The melting point of a mixture of the Zn-NaOH and Al-NaOH products was 82° to 84° C. The product melting at 120° to 121° C. appears as an impurity in the preparation of 2,3-diphenylpiperazine. This product will not react with hot hydrochloric or hydrobromic acids. This is substantiated by the fact that the melting point of a mixture of the compound and the product resulting from the acid treatment is not lowered. The substance melting at 120° to 121° C. cannot be reduced to 2,3-diphenylpiperazine by zinc and sodium hydroxide.

An attempt was made to reduce the 2,3-diphenylpyrazine by refluxing with formic acid. Benzil was identified as one of the resulting products.

(20) 2,5-diphenylpiperazine.

Structural Formula

Empirical Formula	$C_{16}H_{16}N_2$
Molecular Weight	236.156
Melting Point	105°-106° C.
Percentage Yield	22 to 40
Percentage of Nitrogen, Theory	11.76
Percentage of Nitrogen, Found	11.88
Recrystallized from	40% alcohol or heptane
Solubility in Water	Insoluble, cold
Solubility in Alcohol	Soluble
Solubility in Ether	Soluble

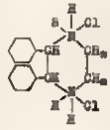
20. 4,5-diphenylpiperazine dihydrochloride.

Seven grams of 4,5-diphenylpiperazine was dissolved in a minimum quantity of 4 normal hydrochloric acid. The solution was carefully evaporated to dryness.

The resulting product was recrystallized from 8 normal hydrochloric acid. It is only slightly soluble in hot absolute alcohol. The dihydrochloride was dried over night at 140° C. and then placed in a vacuum desiccator for 4 days before it was analyzed.

(20) 2,3-diphenylpiperazine dihydrochloride.

Structural Formula

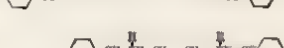


Empirical Formula	$C_{16}H_{18}N_2Cl_2$
Molecular Weight	311.086
Melting Point	320.4°-322.4° C.
Theoretical Yield	8.1
Actual Yield	7.8
Percentage Yield	88
Percentage of Nitrogen, Theory	9.01
Percentage of Nitrogen, Found	8.88
Recrystallised from	6 N Hydrochloric acid
Solubility in Water	Soluble
Solubility in Alcohol	Slightly soluble
Solubility in Ether	Insoluble

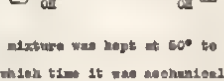
21. N,N'-bis(1,2-diphenyl,2-hydroxyethyl)ethylenediamine dihydrochloride

An attempt was made to synthesize 2,3-diphenylpiperazine by condensing ethylenediamine with benzil and simultaneously reducing the condensation product. However, the product isolated bore no resemblance to 2,3-diphenylpiperazine.

Twenty-five grams of ethylenediamine was diluted with alcohol and neutralized with concentrated hydrochloric acid. This was added to 400 cc. of alcohol containing 40 g. of benzil. Sixty-five grams of zinc and 800 cc. of concentrated hydrochloric acid were added during the course of three hours.



(A)

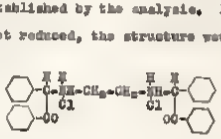


The mixture was kept at 50° to 60° C. for 8 hours during which time it was mechanically stirred. The volume was kept constant by the addition of more alcohol. At the end of 6 hours the hot solution was filtered and then reduced to a volume of approximately 100 cc.

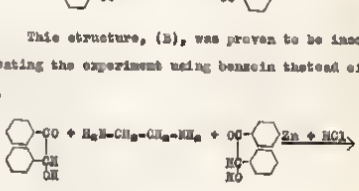
One hundred cc. of water was added and the unreacted benzil was separated by filtration. The volume was reduced to 100 cc. and 50 cc. of alcohol added. White iridescent crystals appeared upon cooling. The crystals were purified, dried over night at 110° C., and placed in a vacuum desiccator for a week.

The structure of the above compound could not be definitely established by the analysis. If the carbonyl groups were not reduced, the structure would be as follows:

(B)



This structure, (B), was proven to be incorrect by repeating the experiment using benzoin instead of benzil.

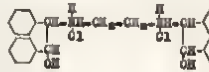


(C)

A mixture of (A) and (C) melted at 254.5° to 255.5° C., the same temperature at which (A) melts.

(21) N,N'-bis(1,2-diphenyl,2-hydroxyethyl)ethylene diamine dihydrochloride

Structural Formula



Empirical Formula	$C_{30}H_{30}N_2O_2Cl_2$
Molecular Weight	525.196
Melting Point	261.5°-262° C.
Theoretical Yield	50 M.
Actual Yield	43.8 M.
Percentage Yield	87
Percentage of Nitrogen, Theory	5.34
Percentage of Nitrogen, Found	5.53
Recrystallized from	75% Alcohol
Solubility in Water	Soluble
Solubility in Alcohol	Slightly soluble
Solubility in Ether	Insoluble

SUMMARY

1. New N-monocarbethoxy piperazine derivatives have been prepared by a method which includes modifications of that used by Jacobi[18] and by Moore, Boyle, and Thorn.[18]

2. New N,N′-dicarbalkoxy compounds have been synthesized and their properties studied, in order that they may be more readily separated from the corresponding N-monoalkoxypiperazine compounds.

3. New N-monoalkyl compounds of piperazine have been made by the use of monocarbethoxypiperazine as an intermediate.

4. New N,N′-dialkyl derivatives of piperazine have been made and their constants determined.

5. The synthesis of 2,5-diphenylpiperazine has been accomplished.

6. N,N′-bis(1,2-diphenyl,2-hydroxyethyl)ethylenediamine dihydrochloride has been made and its structure proven.

BIBLIOGRAPHY

1. Fourneau and Sarrelet, Chemical Abstracts, 24, 3749 (1930)
2. Schmidt and Siehman, Ber. 24, 3237 (1891)
3. Fourneau and Sarrelet, Bull. soc. chim. 45 (4), 1172 (1929)
4. French Patent 398,657
5. Kermack and Smith, J. Chem. Soc., 1929, 1356
6. Kermack and Smith, J. Chem. Soc., 1931, 3006
7. Mousseron, Bull. soc. chim. 51, 782 (1932)
8. Godchot and Mousseron, Compt.rend., 194, 619 (1932)
9. Prelog and Driza, Collection of Czechoslovak Chemical Communications, 5, 497 (1933)
10. Pollard and VanDowell, J. Am. Chem. Soc., 56, 2196 (1934)
11. Pollard and Adelson, J. Am. Chem. Soc., 56, 150 (1934)
12. Soyre, Coyle and Thorn, J. Chem. Soc., 1932, (1) 89
13. Richter's, Organic Chemistry, (translated by D'Albe) 3, 206
19. Prelog and Otegan, Collection of Czechoslovak Chemical Communications, 7, 99 (1935)
18. Jacobi, Ber. 66, 115 (1933)
19. Rosdalsky, J. Chem. Soc., 70 (1) 257 (1896)
J. pr. Chem. (2) 53 19 (1899)

17. Van Dorp, Rec. trav. chim., 28, 68

18. D.R.P.A.G. 9457. Schmidt and Siekmann, Ber. 24, 3246 (1891)

19. Ladenburg, Ber. 24, 2401 (1891)

20. Knorr, Ber. 37, 3507 (1904)

21. Hofmann, Jahresberichte uber die Fortschritte der Chemie, 1869, 389

22. Forese and Pollard, J. Am. Chem. Soc., 57, October (1935)

23. Mason, Ber. 20, 268 (1887)

24. Bernthsen and Sudborough, Text-Book of Organic Chemistry (D.Van Nostrand Co.) 389

25. German Patent, 143,187

26. Lukens, Ind. Eng. Chem. 13, 668 (1921)

27. Wagner, J. Am. Chem. Soc., 54, 680 (1932)

28. German Patent 437,975

29. Mailhe, Bull. soc. chim. 25, 321 (1919)

30. Wheeler and Smith, J. Chem. Soc., 41, 1062 (1919)

31. Clark, The Determination of Hydrogen Ions (Williams and Williams) 106 (1925)

32. J. Am. Chem. Soc., 57, 1st page, May issue, (1935)

ACKNOWLEDGMENTS

The author wishes to express his appreciation and indebtedness for the advice and assistance of Dr. C. B. Pollard, under whose direction this research was conducted. To fellow research workers, whose co-operation and helpful suggestions served to make this work easier and more pleasant, the writer also wishes to extend his thanks.

BIOGRAPHY

Allen T. Cole was born January 9, 1909 at Minnesota Lake, Minnesota. He attended Hamline University, St. Paul, Minnesota and graduated with the degree of Bachelor of Science in 1930. He has attended the Graduate School of the University of Florida from 1931 to 1935 and received the degree of Master of Science in 1933. He was a graduate assistant in the Chemistry Department of the University of Florida from 1931 to 1935.

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee, and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

Date August 30, 1935

James M. Anderson
Dean

Supervisory Committee:

[signature]
Chairman

[signature]

[signature]

[signature]

[signature]